

The mean IMX-SEV-3b score of the 29-gene host response classifier was significantly lower (0.58) in survivors compared to non-survivors (0.66) in ICU patients with COVID-19

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A Transcriptomic Severity Classifier IMX-SEV-3b to Predict Mortality in Intensive Care Unit Patients with COVID-19: A Prospective Observational Pilot Study

INTRODUCTION

The prediction of disease outcomes in COVID-19 patients in the ICU is of critical importance, and the examination of host gene expressions is a promising tool. The 29-host mRNA Inflammation-Severity-3b (IMX-SEV-3b) classifier has been reported to predict mortality in emergency department COVID-19 patients and surgical ICU patients. The accuracy of the IMX-SEV-3b in predicting mortality in COVID-19 patients admitted to the ICU is yet unknown.

OBJECTIVES

Our aim was to investigate the accuracy of the IMX-SEV-3b in predicting the ICU mortality of COVID-19 patients. In addition, we assessed the predictive performance of routinely measured biomarkers and the Sequential Organ Failure Assessment (SOFA) score as well.

METHODS

- This was a prospective observational study enrolling COVID-19 patients who received mechanical ventilation on the ICU of the Erasmus MC, the Netherlands.
- The IMX-SEV-3b scores were generated by amplifying 29 host response genes from peripheral blood collected in PAXgene® Blood RNA tubes.
- A severity score was provided, ranging from 0 to 1 for increasing disease severity.
- The primary outcome was the accuracy of the IMX-SEV-3b in predicting ICU mortality, and we calculated the AUROC of the IMX-SEV-3b score, the biomarkers CRP, D-dimer, ferritin, leukocyte count, IL-6, LDH, neutrophil-to-lymphocyte ratio, procalcitonin and the SOFA score.

CONCLUSIONS

In this observational pilot study, the mean IMX-SEV-3b score of the 29-gene host response classifier was significantly lower (0.58) in survivors compared to non-survivors (0.66). The AUROCs of the IMX-SEV-3b and the assessed biomarkers failed to achieve statistical significance in predicting mortality within this COVID-19 patient cohort, in contrast to the SOFA score, which did exhibit statistical significance. Further prospective studies are required to test the IMX-SEV-3b classifier in the ICU.

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RESULTS

A total of 53 patients were included between 1 March and 30 April 2020, with 47 of them being included within 72 h of their admission to the ICU. Of these, 18 (34%) patients died during their ICU stay, and the IMX-SEV-3b scores were significantly higher in non-survivors compared to survivors (0.65 versus 0.57, p = 0.05) (table 1). The AUROC for prediction of ICU mortality by the IMX-SEV-3b was 0.65 (0.48–0.82) (table 2). The AUROCs of the biomarkers ranged from 0.52 to 0.66, and the SOFA score had an AUROC of 0.81 (0.69–0.93). The AUROC of the pooled biomarkers CRP, D-dimer, ferritin, leukocyte count, IL-6, LDH, NLR and PCT for prediction of ICU mortality was 0.81 (IQR 0.69–0.93). The specificity of the ‘rule-in’ Very High, High and Moderate interpretation bands was, respectively, 100%, 94% and 74%, and the sensitivity of the ‘rule-out’ Very Low and Low interpretation bands was 100% and 56% (table 3).

Table 2. AUROCs of biomarkers, SOFA and IMX-SEV-3b.

Test/biomarker/clinical score	AUROC (95% CI)
CRP (mg/L)	0.52 (0.34-0.70)
D-dimer (mg/L)	0.62 (0.45-0.79)
Ferritin (mg/L)	0.58 (0.42-0.75)
Leukocyte count (x10 ⁹ /L)	0.66 (0.48-0.83)
IL-6 (pg/mL)	0.58 (0.40-0.76)
LDH (U/L)	0.56 (0.37-0.74)
NLR	0.60 (0.43-0.78)
PCT (ng/mL)	0.59 (0.43-0.76)
IMX-SEV-3b	0.65 (0.48-0.82)
SOFA score	0.81 (0.69-0.93)
Pooled biomarker model	0.81 (0.69-0.93)

CRP: c-reactive protein. IL-6: interleukin-6; LDH: lactate dehydrogenase. NLR: neutrophil to lymphocyte ratio; PCT: procalcitonin. SOFA: sequential organ failure assessment. The pooled biomarker model included the biomarkers CRP, D-dimer, Ferritin, Leukocyte count, IL-6, LDH, NLR and PCT.

Table 1. Biomarkers, SOFA and IMX-SEV-3b scores at inclusion.

Characteristics	All Patients n = 53	Survivors n = 35	Non-Survivors n = 18	p-Value
CRP (mg/L)	277 (178–345)	304 (174–341)	210 (178–347)	0.74
D-dimer (mg/L)	2.48 (1.38–5.22)	2.42 (1.18–3.96)	3.86 (1.81–8.47)	0.17
Ferritin (mg/L)	1580 (974–2680)	1660 (1130–2730)	1300 (989–2240)	0.33
Leukocyte count (x 10 ⁹ /L)	8.74 (6.53–10.7)	8.31 (6.47–9.53)	10.30 (7.57–12.30)	0.06
IL-6 (pg/mL)	161 (88–307)	143 (91.5–246)	197 (87.3–395)	0.36
LDH (U/L)	322 (271–394)	320 (264–360)	341 (293–456)	0.06
NLR	7.45 (4.78–10.7)	6.72 (4.69–9.92)	8.85 (5.03–12.40)	0.22
PCT (ng/mL)	0.97 (0.470–2.70)	0.77 (0.36–2.04)	1.44 (0.90–3.20)	0.28
SOFA score	7.00 (6.00–10.00)	7.00 (6.00–8.00)	11.00 (9.00–11.00)	<0.001
IMX-SEV-3b score *	0.582 ± 0.13	0.575 ± 0.11	0.660 ± 0.15	0.050

CRP: C-reactive protein. LDH: lactate dehydrogenase. IL-6: interleukin-6. NLR: neutrophil-to-lymphocyte ratio. PCT: procalcitonin. SOFA: Sequential Organ Failure Assessment. * Mean ± SD; all others are reported as median (IQR).

Table 3. Performance of the IMX-SEV-3b in predicting ICU mortality.

IMX-SEV-3b Severity Score	Survival Status		IMX-SEV-3b Performance per Band			
	Survivor	Non-Survivor	% Patients in Band	Sensitivity	Specificity	Likelihood Ratio
Very High	0	4	8%	22%	100%	Inf.
High	2	0	4%	0%	94%	0.00
Moderate	9	6	28%	33%	74%	1.30
Low	23	8	58%	56%	66%	0.68
Very Low	1	0	2%	100%	3%	0.00

Inf: infinite.